Opioid agonist treatment dosage and patient-perceived dosage adequacy, and risk of hepatitis C infection among people who inject drugs

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ABSTRACT

BACKGROUND: Opioid agonist treatment is considered important in preventing acquisition of hepatitis C virus (HCV) among people who inject drugs; however, the role of dosage in opioid agonist treatment is unclear. We investigated the joint association of prescribed dosage of opioid agonist treatment and patient-perceived dosage adequacy with risk of HCV infection among people who inject drugs.

METHODS: We followed prospectively people who inject drugs at risk of acquiring HCV infection (who were RNA negative and HCV-antibody negative or positive) in Montréal, Canada (2004–2017). At 6-month, then 3-month intervals, participants were tested for HCV antibodies or RNA, and completed an interviewer-administered behavioural questionnaire, reporting the following: current exposure to opioid agonist treatment (yes/no), pre-

scribed dosage either high (methadone ≥ 60 mg/d or buprenorphine ≥ 16 mg/d) or low, and perceived dosage adequacy (adequate/inadequate). We then assigned participants to 1 of 5 exposure categories: no opioid agonist treatment, high dosage of opioid agonist treatment perceived to be adequate, high dosage perceived to be inadequate, low dosage perceived to be adequate or low dosage perceived to be inadequate. To estimate associations between categories of opioid agonist treatment dosage and incident HCV infection, we conducted Cox regression analyses, adjusting for multiple confounding factors.

RESULTS: Of 513 participants (median age 35.0 yr, 77.6% male), 168 acquired HCV over 1422.6 person-years of follow-up (incidence 11.8/100 person-years, 95% confidence interval [CI] 10.1–13.7). We

observed a gradient in the relative risks of HCV infection across categories of opioid agonist treatment dosage. Compared with people who inject drugs not receiving opioid agonist treatment, adjusted hazard ratios were 0.43 (95% CI 0.23–0.84) for those receiving high dosages perceived to be adequate, 0.61 (95% CI 0.25–1.50) for those receiving high dosages perceived to be inadequate, 1.22 (95% CI 0.74–2.00) for those receiving low dosages perceived to be adequate and 1.94 (95% CI 1.11–3.39) for those receiving low dosages perceived to be inadequate.

INTERPRETATION: Risk of HCV infection varies considerably according to dosage of opioid agonist treatment and patient-perceived adequacy, with associations indicating both protective and harmful effects relative to no exposure to opioid agonist treatment.

I n North America, rising incidence of hepatitis C virus (HCV) has tracked the opioid epidemic. From 2004 to 2014, a twofold increase in the annual incidence of acute HCV infection was documented in the United States, mirroring increases in treatment admissions characterized by opioid injection throughout the same period.[1] In Montréal, Canada, our group documented that injection of prescription opioids tripled during 2004–2009 among people who inject drugs followed in the Montreal Hepatitis C Cohort (HEPCO), and this practice was linked to a nearly twofold greater risk of HCV infection relative to injection of other drugs.[2]

Pharmacotherapy with opioid agonist treatment, the recommended first-line treatment for opioid use disorder,[3] can prevent

HCV infection, with an estimated average risk reduction of 50%.[4] The role of dosage of opioid agonist treatment in moderating this relation is unclear, however.[4] Higher dosages (≥ 60 mg/d for methadone and ≥ 12–16 mg/d for buprenorphine), which are typically recommended by clinical practice guidelines for the management of opioid use disorders,[3,5–7] are more effective in promoting treatment retention and reducing withdrawal and illicit opioid use.[8–11] Increasing evidence also highlights the importance of patients' subjective perceptions of their dosage of opioid agonist treatment in influencing treatment outcomes, irrespective of prescribed dosage. Perceptions of adequate dosage have been linked to reduced opioid craving and poly-drug use,[12] greater treatment adherence[13] and

willingness to continue treatment.[14] Yet, many patients receive dosages lower than those considered clinically optimal or dosages that they perceive to be inadequate.[14–16]

In the context of an ongoing global movement to eliminate HCV as a public health threat by 2030,[17] and in light of evidence that scale-up of opioid agonist treatment will be central to achieving this goal,[18] this study seeks to improve our understanding of how to optimize provision of opioid agonist treatment for the prevention of HCV transmission. We aimed to investigate the joint association of prescribed dosage of opioid agonist treatment and patient-perceived dosage adequacy with the risk of HCV infection among people who inject drugs.

Methods

Study design and sample

We used observational data collected in HEPCO, a prospective cohort established in Montréal in 2004 to assess determinants of HCV infection among people who inject drugs. Our recruitment and follow-up criteria have been previously published.[19,20] HEPCO recruits participants through street-level strategies and community-program referrals. To be eligible, participants must report having injected drugs within the previous 6 months and be 18 years of age or older. Initially, only HCV-seronegative participants, at risk of primary HCV infection, were recruited. Since 2011, recruitment expanded to include HCV-seropositive, RNA-negative people who inject drugs, who had cleared their infection and were at risk of re-infection. Eligibility for the present study was restricted to HEPCO participants who reported using opioids or taking opioid agonist treatment at least at 1 study visit, and who had a minimum of 2 total visits.

Cohort visits were scheduled at 6-month intervals up to 2011 and at 3-month intervals thereafter, consistent with the need for more frequent testing intervals to assess HCV re-infection.[21] Visits consisted of answering an interviewer-administered questionnaire and HCV antibody or RNA testing. Participants were asked to return for their test results 2 weeks after each visit for posttest counselling and service referrals. Those who did not report any injection drug use throughout a cumulative period of 24 months were no longer followed. Participants signed an informed consent in compliance with institutional review board regulations of the Centre hospitalier de l'Université de Montréal and received a small stipend (Can$15–$20) at each visit.

Measures

Exposure

At each visit, participants reported current enrolment in an opioid agonist treatment program (yes/no), prescribed dosage (mg/d) and perceived dosage adequacy (adequate/too low/too high). In line with opioid agonist treatment guidelines for the management of opioid use disorders[3,5–7] and similar to a previous study,[22] we categorized a prescribed opioid agonist treatment dosage as "high" if the prescription was methadone 60 mg/d or greater or buprenorphine (combined with naloxone) 16 mg/d or greater, and low otherwise. We further stratified perceived dosage adequacy as adequate or inadequate, the latter category being applied to participants who reported their dosage as too high or too low. We assigned each

participant to 1 of 5 exposure categories: no opioid agonist treatment, high dosage of opioid agonist treatment perceived to be adequate, high dosage perceived to be inadequate, low dosage perceived to be adequate or low dosage perceived to be inadequate.

In a subanalysis, we replaced high/low categories informed by thresholds specified a priori, with high/moderate/low categories based on tertiles observed in our sample. This categorization was done to examine the presence of a linear trend between prescribed dosage of opioid agonist treatment and HCV infection, and does not reflect clinically indicated thresholds. In Quebec, opioid agonist treatment is subsidized by the provincial public drug benefit program.

Outcome

The outcome of interest was time to incident HCV infection. Primary infection was defined by the presence of HCV antibodies at a follow-up visit among participants who were previously HCV-antibody negative. Blood specimens yielding positive results for HCV antibodies using enzyme immunoassay (Abbott Laboratories) were confirmed by reverse-transcription polymerase chain reaction (Roche Diagnostic Systems). HCV re-infection was defined as a positive HCV-RNA test at a follow-up visit among participants who were previously HCV-RNA negative. RNA testing was performed using the Qualitative COBAS AMPLICOR Test version 2.0 until 2013, and the COBAS Ampliprep/COBAS TaqMan Quantitative Test version 2.0 (Roche) or the RealTime HCV assay (Abbott) thereafter.

Covariates

We identified potential confounding variables based on previous studies examining the relation between opioid agonist treatment and HCV infection.[23] These included age (yr), sex (male/female), college education (yes/no), injecting duration (yr), past-month cocaine injection (yes/no), past-month unstable housing, past 3- or 6-month incarceration (depending on follow-up period), and previous HCV infection. As previously,[24] unstable housing was defined as living on the street, in shelters or in apartment hotels rented on a monthly basis. Because access to opioid agonist treatment and risk of HCV infection might have changed over time, we also considered follow-up period (2004–2011 v. 2011–2017) as potentially confounding. Opioid injection and injection frequency are postulated to mediate the relation between opioid agonist treatment and risk of HCV infection and were therefore not considered as confounders.

Statistical analysis

For all participants, follow-up started at the first visit at which opioid use or opioid agonist treatment exposure was reported (henceforth, considered baseline) and ended at the time of HCV infection or, alternatively, at the last visit. We estimated the date of HCV infection using the midpoint between the last negative and first positive HCV test.

We first plotted Nelson–Aalen estimators of the cumulative hazard of HCV infection stratified by dosage of opioid agonist treatment. Suitable for a graphic representation of the effects of time-varying exposures, the plot illustrates the estimated number of times one could theoretically acquire HCV during a given period.[25,26] At each time point, the relative risk of HCV infection across any 2 exposure categories can be estimated. Second, we employed time-varying Cox regression models to estimate hazard ratios (HRs) and corresponding

95% confidence intervals (CIs) of associations between dosage of opioid agonist treatment and risk of HCV infection.

A multivariable model was fit, adjusting for injecting duration and sex as a priori confounders, plus any factors identified as potentially confounding, based on a 5% change-in-estimate criterion.[27] With the exception of sex, education and previous HCV infection, we updated all variables at each visit to reflect the most recent information recorded. The linearity assumption for Cox regression was evaluated by plotting martingale residuals for continuous variables.[28] Both age and duration of injection drug use appeared to be linearly related to HCV infection risk and were therefore analyzed in continuous form. Because of correlation between age and injecting duration (Pearson correlation coefficient, $r = 0.70$), only the latter was included in the multivariable model. Missing data were infrequent (< 0.5% for any one variable) and were imputed by the median and modal values for continuous and categorical variables, respectively. Given that it was relatively uncommon for participants to perceive their dosage of opioid agonist treatment as too high if it was perceived to be inadequate (19.7%), we performed subanalyses excluding these observations to aid interpretation. Statistical analyses were performed using SAS version 9.3.

Although no statistical power calculations were conducted for this investigation when designing the HEPCO cohort, we regularly conduct power calculations for key determinants of HCV infection risk. Assuming a sample size of 500 participants and an 80% annual retention, we estimated having adequate power (> 80%) to detect significant associations (2-sided $p < 0.05$) for moderate binary effects (e.g., HR ≥ 1.4).

Ethics approval

The objectives of this study fall within the broader goals of HEPCO, which was approved by the institutional review board of the Centre hospitalier de l'Université de Montréal.

Results

Between November 2004 and August 2017, we recruited 780 people who inject drugs, of whom 604 (77.4%) reported having used opioids or receiving opioid agonist treatment at least at 1 study visit. Of these, 513 (84.9%) completed a minimum of 2 visits and made up our study sample. We found no significant differences between participants who did ($n = 513$) and did not ($n = 91$) have a minimum of 2 visits for most variables, including opioid agonist treatment dosage, except for age and prior HCV infection: participants with at least 2 visits were older (median age 35.0 yr v. 29.0 yr, $p < 0.01$) and more likely to have been infected with HCV previously (30.8% v. 19.8%, $p = 0.03$).

The baseline characteristics of participants, overall and stratified by categories of opioid agonist treatment dosage, are presented in Table 1. Most were male (77.6%), with a median age of

Table 1: Baseline characteristics of people who inject drugs enrolled in the Montreal Hepatitis C Cohort (2004–2017), by prescribed dosage of opioid agonist treatment, categorized according to clinical guideline recommendations* and patient-perceived dosage adequacy

Characteristic	Dosage of opioid agonist treatment and perceived adequacy; no. (%) of participants†					
	Not enrolled in opioid agonist treatment $n = 354$	High dosage, perceived adequate $n = 61$	High dosage, perceived inadequate $n = 25$	Low dosage, perceived adequate $n = 49$	Low dosage, perceived inadequate $n = 24$	p value‡
Age, yr, mean (± SD)	35.8 (± 10.8)	39.5 (± 10.7)	38.4 (± 9.6)	34.9 (± 9.7)	32.3 (± 7.9)	0.02
Age, yr, median (IQR)	33.9 (26.9–44.3)	40.7 (31.1–47.3)	37.5 (32.2–43.0)	33.3 (27.4–42.3)	31.3 (26.7–35.6)	0.03
Sex, male	284 (80.2)	43 (70.5)	16 (64.0)	36 (73.5)	19 (79.2)	0.3
College education or higher	74 (20.9)	22 (36.1)	10 (40.0)	13 (26.5)	11 (45.8)	< 0.01
Duration of injection drug use, yr, mean (± SD)	11.0 (± 10.2)	18.2 (± 9.4)	16.5 (± 11.5)	13.4 (± 9.9)	11.6 (± 8.8)	< 0.01
Duration of injection drug use, yr, median (IQR)	7.8 (2.8–16.2)	18.0 (10.1–26.1)	15.0 (4.7–25.0)	12.3 (4.6–20.3)	9.7 (4.0–16.1)	< 0.01
Opioids injection, past mo	260 (73.4)	33 (54.1)	22 (88.0)	37 (75.5)	22 (91.7)	< 0.01
Cocaine injection, past mo	191 (54.0)	28 (45.9)	8 (32.0)	25 (51.0)	11 (45.8)	< 0.01
High frequency of injection drug use (≥ 30 injections), past mo	208 (58.8)	20 (32.8)	13 (52.0)	22 (44.9)	19 (79.2)	< 0.01
Unstable housing, past mo	147 (41.5)	16 (26.2)	4 (16.0)	8 (16.3)	7 (29.2)	< 0.01
Incarceration, past 3 or 6 mo§	76 (21.5)	12 (19.7)	5 (20.0)	9 (18.4)	7 (29.2)	0.9
Previous HCV infection	76 (21.5)	34 (55.7)	14 (56.0)	25 (51.0)	9 (37.5)	< 0.01
2004–2011 follow-up wave (v. 2011–2017)	199 (56.2)	21 (34.4)	12 (48.0)	27 (55.1)	10 (41.7)	0.02

Note: HCV = hepatitis C virus, IQR = interquartile range, SD = standard deviation.
*Prescribed dosage was categorized as high if methadone ≥ 60 mg/d or buprenorphine ≥ 16 mg/d, and low otherwise.[3,5–7]
†Unless stated otherwise.
‡p value derived from analysis of variance and Kruskal–Wallis test for age and duration of injection, and χ^2 test for all other variables.
§Depending on follow-up wave.

Table 2: Hazard ratios for associations between incident hepatitis C virus infection and prescribed dosage of opioid agonist treatment, categorized according to clinical guideline recommendations* and patient-perceived dosage adequacy

Variable	No. of observations	No. of person-years of follow-up	No. of incident cases	Rate per 100 person-years	Unadjusted HR (95% CI)	Adjusted HR† (95% CI)
Dosage of opioid agonist treatment and perceived adequacy						
Not enrolled in opioid agonist treatment	1831	782.78	118	15.07	1.00 (Ref.)	1.00 (Ref.)
High dosage, perceived adequate	663	274.07	10	3.65	0.28 (0.15–0.54)	0.43 (0.23–0.84)
High dosage, perceived inadequate	214	86.28	5	5.80	0.43 (0.17–1.05)	0.61 (0.25–1.50)
Low dosage, perceived adequate	510	207.15	20	9.65	0.79 (0.49–1.28)	1.22 (0.74–2.00)
Low dosage, perceived inadequate	211	72.32	15	20.74	1.46 (0.85–2.50)	1.94 (1.11–3.39)
Age, yr‡§					0.83 (0.76–0.90)	–
≤ 31.6	856	430.95	86	19.96	–	–
> 31.6–40.4	859	375.57	39	10.38	–	–
> 40.4–48.2	856	326.55	26	7.96	–	–
> 48.2	858	289.53	17	5.87	–	–
Sex						
Female	664	281.18	36	12.80	1.00 (Ref.)	1.00 (Ref.)
Male	2765	1141.41	132	11.56	1.00 (0.69–1.45)	0.74 (0.50–1.10)
College education or higher						
No	2472	1062.6	140	13.18	1.00 (Ref.)	–
Yes	957	359.99	28	7.78	0.55 (0.37–0.82)	–
Duration of injection drug use, yr‡					0.79 (0.72–0.87)	0.85 (0.77–0.94)
≤ 7.2	857	399.79	91	22.76	–	–
> 7.2–15.3	859	403.14	41	10.17	–	–
> 15.3–25.0	856	331.85	22	6.63	–	–
> 25.0	857	287.82	14	4.86	–	–
Cocaine injection, past mo						
No	2088	886.91	52	5.86	1.00 (Ref.)	1.00 (Ref.)
Yes	1341	535.69	116	21.65	3.17 (2.28–4.40)	2.85 (2.04–3.99)
Unstable housing, past mo						
No	2579	1075.58	88	8.18	1.00 (Ref.)	1.00 (Ref.)
Yes	850	347.01	80	23.05	2.34 (1.72–3.17)	2.14 (1.54–2.96)
Incarceration, past 3 or 6 mo¶						
No	3068	1245.82	121	9.71	1.00 (Ref.)	1.00 (Ref.)
Yes	361	176.78	47	26.59	2.32 (1.65–3.27)	1.80 (1.26–2.56)
Previous HCV infection						
No	2148	972.59	138	14.19	1.00 (Ref.)	1.00 (Ref.)
Yes	1281	450	30	6.67	0.43 (0.29–0.64)	0.73 (0.46–1.15)
Follow-up wave						
2004–2011	912	551.26	96	17.41	1.00 (Ref.)	–
2011–2017	2517	871.34	72	8.26	0.64 (0.47–0.87)	–

Note: CI = confidence interval, HCV = hepatitis C virus, HR = hazard ratio, Ref. = reference category.
*Prescribed dosage was categorized as high if methadone ≥ 60 mg/d or buprenorphine ≥ 16 mg/d, and low otherwise.[3,5–7]
†Adjusted for sex (male/female), duration of injection drug use (yr), past-month cocaine injection (yes/no), past-month unstable housing (yes/no), past 3- or 6-month incarceration (yes/no), and previous HCV infection (yes/no).
‡Age and duration of injection drug use were analyzed in continuous form in Cox regression models. Hazard ratios represent the effect of a 5-year increase.
§Because of correlation with duration of injection drug use (Pearson correlation coefficient, r = 0.70), this variable was not entered in the multivariable Cox regression model.
¶Depending on follow-up wave.

35.0 years and median duration of injection drug use of 9.5 years. Among participants enrolled in opioid agonist treatment (*n* = 159), 61 (38.4%) had a high dosage that they perceived to be adequate, 25 (15.7%) had a high dosage perceived to be inadequate, 49 (30.8%) had a low dosage perceived to be adequate, and 24 (15.1%) had a low dosage perceived to be inadequate.

The median number of study visits per participant was 6 (interquartile range 3–10). Over a total observation period of 1422.6 person-years of follow-up, 168 participants (32.7%) acquired HCV, for an incidence rate of 11.8 per 100 person-years (95% CI 10.1–13.7).

Table 2 presents crude and adjusted HRs for associations between dosage of opioid agonist treatment and risk of HCV infection relative to no exposure to opioid agonist treatment. We observed a gradient in the relative risk of HCV infection across the 4 categories of opioid agonist treatment dosage. In multivariable analyses, people who inject drugs who had a high dosage of opioid agonist treatment that they perceived to be adequate had the lowest risk of HCV infection (adjusted HR 0.43, 95% CI 0.23–0.84). In those with a high dosage of opioid agonist treatment perceived to be inadequate and with a low dosage perceived to be adequate, the risk of HCV infection was lower (adjusted HR 0.61, 95% CI 0.25–1.50) and slightly higher (adjusted HR 1.22, 95% CI 0.74–2.00), respectively, relative to people who inject drugs not receiving opioid agonist treatment, yet these estimates were imprecise and nonsignificant. For those with a low dosage of opioid agonist treatment perceived to be inadequate, the risk of HCV infection was nearly twofold greater (adjusted HR 1.94, 95% CI 1.11–3.39) relative to those not receiving opioid agonist treatment.

Results were comparable in subanalyses excluding observations in which opioid agonist treatment dosage was perceived to be too high (data not shown). In subanalyses replacing high/low categories of prescribed opioid agonist treatment dosage with high/moderate/low categories based on tertiles, we noted a linear trend between dosage and risk of HCV infection (Table 3). Nelson–Aalen curves showed a gradient in the cumulative hazard of HCV infection across categories of opioid agonist treatment dosage, mirroring results from Cox regression analyses (Figure 1).

Interpretation

In our study, we found that, compared with no opioid agonist treatment, exposure to a high dosage of opioid agonist treatment (methadone ≥ 60 mg/d or buprenorphine ≥ 16 mg/d) is associated, on average, with a 60% lower risk of infection if the dosage is perceived to be adequate. In contrast, relative to no opioid agonist treatment, exposure to a low dosage of opioid agonist treatment is associated with a twofold greater risk of HCV infection if the dosage is perceived to be inadequate. Exposure to a high dosage perceived to be inadequate and a low dosage perceived to be adequate did not significantly influence HCV risk relative to no exposure to opioid agonist treatment. However, taken together, estimates were consistent with a graded effect of prescribed dosage of opioid agonist treatment and patient-perceived dosage adequacy on risk of HCV infection. Importantly, our findings are indicative of the potential for both protective and harmful effects of opioid agonist treatment dosage, depending on these factors.

The only other study to have compared risk of HCV infection in relation to prescribed dosage of opioid agonist treatment documented a similar reduction in risk for people who inject drugs receiving low (HR 0.58) and high dosages (HR 0.68), relative to those not receiving opioid agonist treatment, yet neither association was significant.[22] Data are lacking on the role of patients' perceptions of the dosage adequacy of opioid agonist treatment in HCV prevention among people who inject drugs. However, accumulating evidence supports the role of patients' perceptions of opioid agonist treatment adequacy in driving favourable outcomes,[12–14] and these are increasingly recognized as a valuable complement to providers' perspectives in defining targets for optimal treatment.[29]

Although our findings suggest that exposure to a high dosage of opioid agonist treatment that is also subjectively perceived as adequate is most likely to confer an HCV-prevention benefit, it remains to be established how to balance clinically recommended dosages with patients' preferences. If a low dosage is perceived to be adequate by patients, and an increase is not desired, the potentially limited benefit to HCV prevention conferred through opioid

Table 3: Hazard ratios for associations between incident hepatitis C virus infection and prescribed dosage of opioid agonist treatment, categorized according to tertiles* and patient-perceived dosage adequacy

Dosage of opioid agonist treatment and perceived adequacy	No. of observations	No. of person-years of follow-up	No. of incident cases	Rate per 100 person-years	Unadjusted HR (95% CI)	Adjusted HR† (95% CI)
Not enrolled in opioid agonist treatment	1831	782.78	118	15.07	1.00 (Ref.)	1.00 (Ref.)
High dosage, perceived adequate	390	167.10	4	2.39	0.18 (0.07–0.50)	0.27 (0.10–0.74)
High dosage, perceived inadequate	113	49.90	2	4.01	0.32 (0.08–1.28)	0.37 (0.09–1.49)
Moderate dosage, perceived adequate	402	156.06	12	7.69	0.59 (0.32–1.07)	0.93 (0.50–1.72)
Moderate dosage, perceived inadequate	139	49.28	6	12.18	0.83 (0.37–1.89)	1.40 (0.61–3.24)
Low dosage, perceived adequate	381	158.05	14	8.86	0.75 (0.43–1.31)	1.21 (0.68–2.14)
Low dosage, perceived inadequate	173	59.41	12	20.20	1.42 (0.78–2.58)	1.95 (1.06–3.59)

Note: CI = confidence interval, HR = hazard ratio, Ref. = reference category.
*Prescribed dosage was categorized as high if methadone > 80 mg/d or if buprenorphine > 14 mg/d; moderate if methadone > 45 and ≤ 80 mg/d, or if buprenorphine > 8 and ≤ 14 mg/d; and low if methadone > 0 and ≤ 45 mg/d, or if buprenorphine > 0 and ≤ 8 mg/d.
†Adjusted for sex (male/female), duration of injection drug use (years), past-month cocaine injection (yes/no), past-month unstable housing (yes/no), past 3- or 6-month incarceration (yes/no), and previous HCV infection (yes/no).
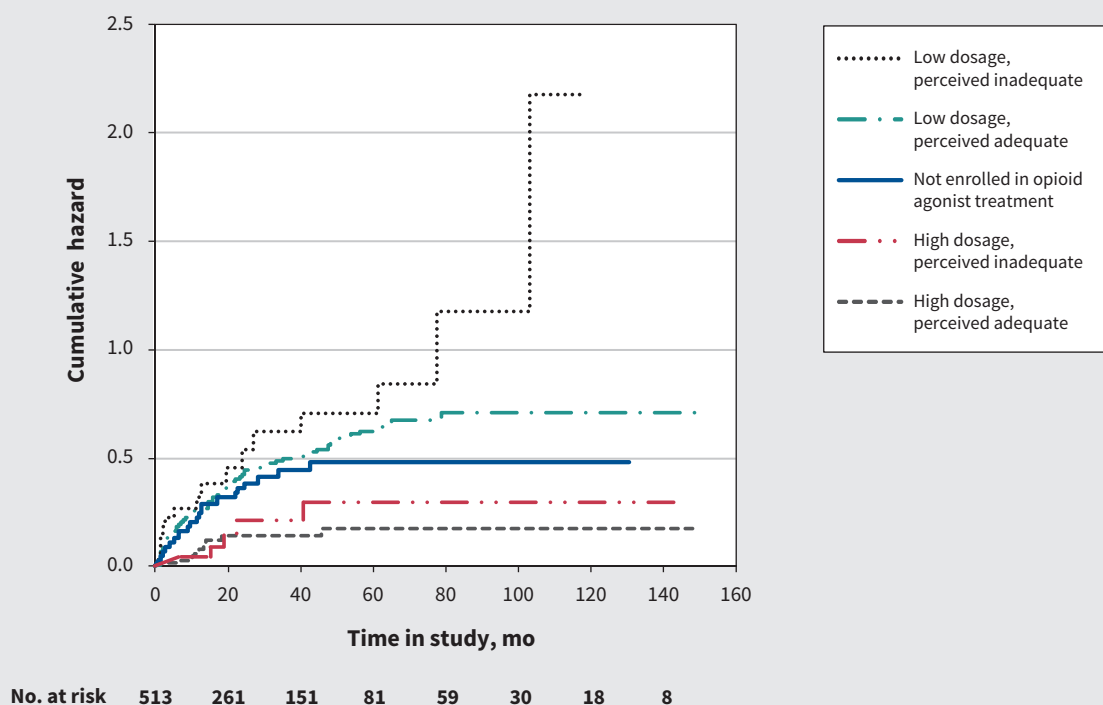
Figure 1: Nelson–Aalen estimates of the cumulative hazard of hepatitis C virus infection according to prescribed dosage of opioid agonist treatment and patient-perceived dosage adequacy.

agonist treatment should be discussed. Our finding of a nearly twofold greater risk of HCV infection among people who inject drugs receiving a low and subjectively inadequate dosage of opioid agonist treatment, compared with those not enrolled in opioid agonist treatment, is particularly worrisome. For most participants in our study, dosages of opioid agonist treatment that were perceived to be inadequate were reportedly too low. This inadequate dosing could lead to increased illicit drug use and risk behaviours,[9] potentially explaining the greater risk of HCV infection.

Although further research is needed to explore reasons leading to low or inadequate dosing of opioid agonist treatment, prior studies have flagged social stigma surrounding this treatment[14] and abstinence-oriented ideologies among prescribers and treatment settings as potential drivers.[15] Altogether, our study supports the need to ensure that opioid agonist treatment programs provide care following best-practice guidelines and that clinicians work with patients to identify a suitable dosage that is most likely to be clinically effective while meeting their individual needs.

Limitations

Our study had several limitations. First, residual confounding of the estimated associations cannot be ruled out, despite our efforts to adjust for known confounders. For example, the reduced risk of HCV infection observed among people who inject drugs whose dosage of opioid agonist treatment was high and perceived to be adequate could be partly attributed to having greater motivation to reduce risk behaviours relative to other participants. Second, selec-

tion bias as a result of losses to follow-up may have affected our estimates. Our follow-up rates are good for a population of people who inject drugs, however, and participants lost to follow-up were similar to those retained with respect to most baseline characteristics, diminishing the likelihood of this risk. Third, because it was based on self-report, misclassification of opioid agonist treatment dosage is possible. However, in one study involving people who inject drugs in Amsterdam, authors validated self-reported methadone dosage and found excellent correlation between self-report and prescription registry data.[30] Finally, our focus on the joint effect of 2 measures of opioid agonist treatment dosage on HCV infection risk may have limited our power to detect significant associations, particularly for the category of high dosages perceived to be inadequate, which had few events.

Conclusion

Risk of HCV infection varies substantially according to a combined indicator of opioid agonist treatment dosage informed by prescribed dosage and patients' perceptions. Our results suggest that, to benefit from a lower risk of HCV infection while taking opioid agonist treatment, people who inject drugs must be prescribed a high dosage that they also perceive to be adequate. In light of ongoing calls to broaden access to opioid agonist treatment globally to foster elimination of HCV, our findings suggest that simply expanding access may not be enough and that ensuring adequate dosage of opioid agonist treatment should be central to any HCV-prevention strategy.

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